(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 298 585 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **20.10.93** (51) Int. Cl.5: **A61M 5/28**, A61M 5/315

(21) Application number: **88304091.7**

(22) Date of filing: **06.05.88**

(54) **Syringe.**

(30) Priority: **08.07.87 US 72015**

(43) Date of publication of application:
11.01.89 Bulletin 89/02

(45) Publication of the grant of the patent:
20.10.93 Bulletin 93/42

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
DE-A- 1 766 151
US-A- 3 437 090
US-A- 3 785 379
US-A- 4 424 057
US-A- 4 445 895
US-A- 4 581 023

(73) Proprietor: **DUOJECT MEDICAL SYSTEMS INC**
Suite 308
4920 de Maisonneuve Street
West Montreal Quebec H3Z 1N1(CA)

(72) Inventor: **Reynolds, David L.**
Suite 400
2000 West Broadway
Montreal Quebec, H4B 2A2(CA)

(74) Representative: **Newby, John Ross et al**
J.Y. & G.W. Johnson
Furnival House
14/18 High Holborn
London WC1V 6DE (GB)

Rank Xerox (UK) Business Services
(3.10/3.6/3.3.1)

EP 0 298 585 B1

EV037583070 US

Description

This invention relates to a method of producing prefilled syringes for use in medical or veterinary treatment.

There has been an increasing trend in recent years to the putting up of pharmaceuticals in dosage forms so as to minimize the preparation required to administer a medicament to a patient and to reduce the chances of dosage errors or contamination. One dosage form which has been gaining rapid acceptance is the prefilled disposable syringe. Various difficulties are however associated with the preparation and usage of such syringes, particularly in the case of preparations which, in ready to use condition, have a short shelf life. Numerous forms of dual compartment syringe structure have been proposed for the shipping of such preparations with components stored in separate compartments for admixture immediately prior to use. Although certain structures have met with some degree of acceptance, they are commonly difficult to manufacture and/or use because of difficulties in filling the syringe with the components, and because they require extensive manipulation immediately prior to use. Moreover they are frequently substantially more bulky than conventional syringes because in many cases they frequently comprise components which effectively represent two syringes in tandem.

Problems in the manufacture of prefilled syringes are not confined to two component systems and even with single component systems the filling of syringes under factory conditions is difficult to mechanize effectively and requires expensive special purpose syringe filling machinery. The same applies to related units prefilled with liquids required for injection or infusion during medical procedures.

Another approach where single component systems are involved is exemplified by British Patent Specifications Nos. 1,252,306 and 1,444,119, and U. S. Patent No. 4,445,895, in which a prefilled cartridge having a displaceable plug at one end, and a needle penetrable closure at an opposite end, is inserted into the barrel of a syringe for dispensing of its contents. Whilst such cartridges and the equipment for filling them are known and available, they are only really suitable for preparations which can be stored in liquid form, and require either a special or a modified syringe for their use.

In a further arrangement disclosed in U. S. Patent No. 3,845,763, a cartridge or vial is closed at its bottom end by a slidable plug with a downwardly extending stem, which cartridge or vial is inserted bottom end first into a special holder which carries a double ended needle, so that the stem is penetrated by the needle and the body of the vial is converted into a plunger which can be depressed to expel the contents of the vial through the stem. The projecting stem means that the vial cannot be filled utilizing conventional vial filling machinery.

The present invention seeks to provide a system for the distribution of preparations required for injection or infusion in liquid dosage form during medical procedures, which has a wide range of utility both for single component liquid preparations or for two component systems of which one component may be a solid, which utilizes a small number of components all suitable for mass production, and which is simple to assemble and fill utilizing available equipment.

The invention is based upon the use of vials designed so that they may be filled utilizing conventional filling machinery and techniques, yet also form the barrel of a syringe in a prefilled syringe system which can be adapted for the dispensing of single or two component systems, including two component systems of the kind in which the solid component is lyophilized in situ during manufacture of the syringe.

In the context of the invention, it should be understood that "vial" refers to a particular type of container, having a rather squat cylindrical body whose height compared to the diameter of its base is such that it may stand stably on its base whilst being conveyed through a vial filling machine and subsequently sealed and capped. A vial has a neck with a large enough internal diameter to permit filling from a vial filling machine: solid filling materials will normally require a larger neck than liquids. Vials should not be confused with cartridges, which are comparatively long and slim, and cannot usually be filled utilizing vial filling machinery since they are too tall to rest stably on their bases.

DE-A-1766151 discloses a syringe body closed at one end with a piston, through which material can be passed into the syringe body and to which a plunger can be connected and this document forms the basis for the pre-characterising passage of the following claim 1.

Whilst describing how the syringe is used, DE-A-1766151 is wholly silent as to how it would be assembled and filled. The described embodiments of the syringe exhibit physical features which appear to indicate that the syringe must be filled through the open end of the body prior to insertion of the piston, and that assembly would require to be effected either manually or by means of specialised machinery. This document does not provide any solution to the problem of economical production of prefilled syringes.

What constitutes our invention is defined in claim 1.

The differences between a vial as featured in a syringe produced according to claim 1 and a conventional vial do not prevent it from being filled and capped in conventional vial filling and capping machinery; indeed, apart from the replacement of the bottom wall of the vial by a piston as specified, it is a conventional vial, and can be handled normally by the machinery during filling with either liquid or solid material. Furthermore, liquid filled vials may be lyophilized utilizing special stoppers either as known in the art or as described below.

Desirably the syringe includes as well as the vial and plunger means connected to said piston, an outer cap which can be engaged over the cap of said vial, the outer cap having a hollow needle projecting axially within the cap and a coupling for engagement with injection means and communicating with said hollow needle, the outer cap being axially movable relative to said cap of the vial from a position in which the needle ends short of the cap of the vial to a position in which it penetrates the cap of the vial, and both the plunger means and the outer cap being provided with radially extending flanges for sustaining actuating forces applied to the syringe.

In a syringe for a two component medicament, it is necessary to provide for packaging of the second component and its admixture with the first component in the vial prior to dispensing. This can be achieved using a capsule assembly comprising a generally cylindrical sealed capsule having walls formed of a flexible needle penetrable material, a generally cylindrical neck defined by said walls at one end of the capsule, said neck having axially spaced inner and outer peripheral ridges, and a generally cylindrical cap applied to said neck so that a detent within the cap engages the outer peripheral ridge on the neck, a double ended hollow needle passing through said cap so that an inner end within the cap ends short of the neck of the capsule and an outer end extends outwardly of the cap, the cap being displaceable relative to the capsule to a position in which the detent rides over the inner ridge and the inner end of the needle penetrates the neck of the capsule, the cap and capsule being of a diameter such that they can enter the tubular plunger to a position in which the outer end of the needle on the cap of the capsule penetrates the septum of the piston when the plunger is engaged with the latter.

A syringe prefilled according to the method of the invention can be used to form injection systems for preparations requiring shipping and storage as two separate components, certain subsequences themselves having utility respectively as injection systems for single component liquid preparations. "Injection" is utilized broadly to cover hypodermic, intramuscular and intravenous injection, gravity and mechanical infusion, and injection into other vessels utilized in medical treatment or testing. For the purposes of description, the "front" of an injection system will be considered the end of the system from which a liquid preparation is so injected.

The arrangement including the capsule assembly has a number of advantages in the manufacture of prefilled syringes according to the invention for two component systems; furthermore, without the third cap and the sealed capsule containing the second component the remaining components provide, advantages in the manufacture of prefilled syringes for single component systems. The third cap and sealed capsule provide an advantageous subsystem for various applications in which a sealed sterile source of a liquid is required for injection, or dropwise introduction into other containers used in medical procedures. With prefilled syringes for two components systems, either the capsule or the capsule and the third cap, may be sold, or shipped separately. This enables different diluents or sizes of capsule to be selected, or a common set of diluent capsules to be utilized with syringe assemblies containing different first components, thus simplifying inventory control.

Further features of the invention will become apparent from the following description of a preferred embodiment thereof with reference to the accompanying drawings.

In the drawings:

Figure 1 is a perspective exploded view of the mechanical components of a syringe system capable of being prefilled by the method in accordance with the invention;

Figure 2 is a partially longitudinally sectioned, partially exploded view of the syringe components showing some further details of their construction;

Figures 3, 4 and 5 illustrate preparation of the syringe system to provide a syringe ready for use;

Figures 6, 7 and 8 illustrate exemplary applications of the syringe;

Figures 9 and 10 illustrate an optional feature of a syringe produced in accordance with the invention; and

Figures 11 and 12 are respectively assembled and exploded views of an alternative configuration of the syringe system produced according to the invention.

Referring to Figures 1 and 2, a syringe system for the injection of a liquid preparation stored as two components comprises seven primary mechanical components, apart from the components of the preparation, which latter are shown in Figure 2 but not Figure 1. The components of the preparation typically comprise a first component A which

may be in any physical state suitable for storage in vial, and a second liquid component B, typically but not necessarily sterile water. The liquid component B is stored in a sealed capsule 14 of flexible material, manufactured using conventional techniques from a material, usually synthetic plastic, which is compatible with the contents of the capsule. The first component is stored in a cylindrical vial 6, typically of glass, and capped by an annular cap 4 which retains a conventional needle penetrable sealing member accessible through a central opening in the cap. By a vial is meant a cylindrical vessel which can assume a stable upright position supported by its base, the overall height of the vessel preferably not exceeding 2.5 times the external diameter of the rim of its base so that it remains stable when passing through conventional vial filling and capping equipment utilized to fill and cap the vial. A neck at the upper end of the vial 6, which is capped by the cap 4, has a relatively large internal diameter characteristic of such vessels, usually not less than about 7.5 mm for liquid or 10 mm for solids, so that filling either liquids or solids can be readily achieved. The cap 4 is formed by a soft aluminum sleeve, having a flange retaining a sealing member formed by a soft rubber disc or plug 5 over or in the front end opening, and tightly crimped onto a neck at the front end of the vial so as to seal the latter. A major difference from conventional vials is that the conventional bottom wall of the vial is replaced by an axially movable piston 8 wholly within the vial and in sealing contact with the vial walls. When received within the vial 6, this piston in no way interferes with the handling of the vial using conventional machinery, and in particular permits the vial to be stood on its base with its neck (which forms the front end of the vial when in use) upwards as it passes through the filling and capping equipment.

The filled vial 6 may be converted into a prefilled syringe by applying an outer cap 2 over the cap 4 and positively attaching a cylindrical plunger sleeve 10 to the piston 8. The piston 8, typically formed of rubber, is moulded with a rearward extension 16 with an external thread 18, whilst the interior of the front end of the plunger sleeve 10 is formed with a complementary internal thread 20 so that it may be screwed onto the piston 8. The outer cap 2 fits over the inner cap 4 so that a hollow needle 22 formed within the cap 2 does not reach the plug 5. On the front of the cap 2 and in communication with the hollow needle 22 is a coupling adapter 27, for example similar to those sold under the trade mark **LUER-LOK**, for connection of the syringe to a needle 28 or other instrumentality (see Figures 6-8). The rear ends of both cap 2 and the sleeve 10 are formed with radially extending flanges 24 and 26 respectively which form finger grips for operation of the syringe. Thus if a user grips the syringe by the flanges as shown in Figure 6 and presses them towards each other, the cap 2 is pulled rearwardly onto the cap 4 so that the needle 22 penetrates the plug 5 and the contents of the syringe can be expelled through the needle 22 and the needle 28. It will be noted that the rear end of the vial 6 has a rim 7 formed with only a relatively slight external flange rather than the wide finger flange commonly found on the barrels of conventional syringes. In the present arrangement, the flange 24 provides the function of such a finger flange, enabling the rim 7 to be reduced to a size which will avoid such interference between the rims of adjacent vials as would cause tipping when the vials are conveyed in a vertical attitude through filling and capping equipment.

In many applications, it is desirable to prevent premature penetration of the plug 5 by the needle 22, and therefore the cap 2 may be moulded with short internal threads (not shown) which prevent rearward movement of the cap 2 unless it is twisted so that the threads bite into the soft aluminum of the cap 4 and draw the cap 2 rearwardly so that the needle 22 can penetrate the plug. A prefilled syringe so constructed has significant advantages over conventional prefilled syringes in that the vial may be filled using conventional vial filling equipment, and yet may be utilized directly instead of requiring its contents to be transferred to a syringe prior to use as has been conventional in the use of vials.

The vial may also be charged with material which is not directly injectable, such as solids which must be dissolved or suspended in a liquid medium prior to injection. In this case the liquid medium is sealed as already described in a flexible capsule 14. A third cap 12 is either applied to the capsule as shown in Figure 2, or inserted into the plunger sleeve 10 so that a screw thread 30 on the exterior of the cap engages the screw thread 20 within the sleeve.

A neck 34 of the capsule 14 has two peripheral ridges 36 and 38. If the cap 12 is applied to the capsule, a detent 40 within the cap is pushed over only the outer ridge 38 so that a rear end portion 42 of a hollow needle mounted in the cap stops short of the end of the capsule. By forcing the detent 40 rearwardly over the ridge 36, the needle portion 42 can be forced rearwardly so as to penetrate the capsule. A forward end portion 44 of the hollow needle has a length such that when the cap 12 is screwed into the sleeve 10, and the sleeve 10 is screwed onto the piston 8, the needle portion 44 penetrates a resilient septum 50 normally separating axial passages 46 and 48 formed in the front and rear of the piston.

In use, if the capsule 14 and cap 12 are shipped as a separate unit, this unit is screwed into the sleeve 10 (see Figure 3), and the sleeve 10 is pushed into the rear of the vial 6 so that the needle portion 44 penetrates the septum 50 of the piston 8 and the thread 20 is screwed onto the thread 18 of the piston (see Figure 4). This action also substantially unscrews the cap 12 from the thread 20. The capsule 14 is then pressed forward onto the needle portion 42, and the liquid contents of the capsule can then be squeezed through the needle and into admixture with the first component in front of the piston 8. Thereafter the capsule 14 and cap 12 may be pulled as a unit from the sleeve 10 and discarded (see Figure 5). The septum 50 reseals as the needle portion 44 is withdrawn, leaving a syringe ready for use as illustrated in Figures 6 - 8. Alternatively, if the cap 12 is prefitted to the sleeve, the sleeve 10 may be screwed onto the piston 8, and the capsule 14 pressed into the sleeve 10 and the cap 12 so as to establish communication between the capsule and the space forward of the piston, the procedure thereafter being the same.

Rather than being used conventionally with a needle as shown in Figure 6, the prepared syringe may be used for gravitational or mechanical infusion as shown in Figures 7 and 8. In Figure 7, an adapter 27 is fitted to a complementary coupling on a gravity infuser 52 to provide a drip feed, the sleeve 10 having been unscrewed and discarded, together with the cap 12 and capsule 14, if used. In Figure 8, the syringe is mounted in a mechanical infuser 54 such as that sold under the trade mark **BARD**, the latter being equipped with clamps suited for engagement with the syringe.

By basing the system on an open-bottomed vial 6 closed at its bottom end by a piston 8 equipped with means such as the screw thread 18 for coupling it to a plunger of sleeve form, and with a needle penetrable septum 50, in optional conjunction with sealed flexible capsules of diluent, great flexibility in application can be obtained, using components which are easy to fill, compact to ship, and easy to make ready for use.

Referring now to Figures 9 and 10, the rubber disk or plug retained by the cap 4 on the vial 6 may be replaced by a modified plug 60 as shown in perspective from beneath and one side in Figure 9, and partially installed on a vial 6 in Figure 10. Use of such a plug 60 is advantageous when the solid component of a medicament is to be prepared in situ in the vial by lyophilization. The vial is filled with a liquid preparation to be lyophilized, and plug 60 inserted to the position shown in Figure 10, so that the interior of the vial communicates with its environment through a central passageway 61 and radial bores 62, the passageway and the bores being no larger than needed for the removal of water vapour during lyophilization. The plug is split at 63 to facilitate moulding. After filling the contents of the vial are rapidly frozen and vacuum dried to leave a solid residue in the vial which can be reconstituted immediately before use. The plug 60 is then moved to the full extent permitted by a flange 64 into the neck of the vial 6 and secured by a cap 4. Whilst a conventional lyophilization stopper could be utilized in place of the plug 60, the latter has the advantage of minimizing the amount of liquid trapped within the stopper during use of the syringe. For the same reason, the head of the piston 8 is shaped so as to minimize dead space in the neck of the vial when the contents of the vial are expelled during use of the syringe.

Figures 11 and 12 illustrate an alternate configuration of the syringe. The various components are essentially identical to those already described, and the same reference numerals are utilized except that the outer needle (44) of the conduit extending through the cap (12) is replaced by an extension (70) which is configured at its outer end to couple with a standard syringe coupling such as the coupling (27) on the cap (2). This enables the capsule (14), once inserted in the plunger (10), to be locked through the extension (70) and the coupling (27) to the cap (2) to produce the compact assembly shown in Figure 11. To prepare the syringe for use, the cap (2) is forced rearwardly over the cap (4) so that the needle (22) (see Figure 2) pierces the seal (5), and the capsule (14) is forced forward so that it is pierced by the rear end portion (42) of the needle (44) and its contents can be expelled through the needle (44), the extension (70), the coupling (27) and the needle (22) into the vial (6). The assembly of the capsule (14) and the plunger (10) can then be released from the remainder of the syringe by turning so as to release the extension (70) from the coupling (27), a needle (not shown) may be applied to the coupling (27), the capsule (14) is removed from the plunger (11) and discarded, and the plunger (11) is screwed onto the coupling (18) to ready the syringe for use. With this arrangement, the passages (46 and 48) in the piston (8) are not required.

Claims

1. A method of producing a prefilled syringe for administering a pharmaceutical preparation, said syringe comprising a generally cylindrical syringe body (6) having a neck at a neck end, and a side wall terminating in a rim (7) at a rimmed end, at least a component (A) of the preparation filled into the body (6) via the neck end and sealed in the body (6) with an elastomeric closure (5) closing the body at the neck end and secured by a cap (4), and an

elastomeric piston (8) at the rimmed end forming a hermetic seal with an inside surface of said side wall, needle means (22) for movement relative to the cap (4) to penetrate the elastomeric closure (5), and plunger means (10) for connection to an outer side (16) of the piston, characterised in that the syringe is produced by associating components including said plunger means (10) and said needle means (22) with a prefilled vial (6) produced by; forming said body with a height to diameter ratio such that the body is stable, and so that any outward extent of the rim (7) is insufficient to result in interference such as would cause tipping, when the body is conveyed standing on said rim (7) through equipment for filling and capping pharmaceutical vials; inserting said elastomeric piston (8) wholly within said rimmed end of the body to form a vial (6) open at the neck; and filling said vial through said neck with said pharmaceutical preparation (A), and then applying said elastomeric closure (5) and said cap (4), whilst conveying the vial (6) standing on said rim (7) through equipment for filling and capping pharmaceutical vials.

2. A method according to claim 1, characterised in that said elastomeric closure is configured to vent the vial (6) when partially inserted in said neck, and said elastomeric closure (60) is applied in two stages, in the first of which the closure is partially inserted and the vial (6) thereafter remains vented during lyophilisation of the pharmaceutical preparation filled therein, and a second stage following lyophilisation wherein insertion of the closure (60) is completed.

3. A method according to claim 1 or 2, characterised in that the ratio of the overall height of the body (6) to the external diameter of its rim (7) does not exceed 2.5:1.

4. A method according to any of the preceding claims, characterized in that the neck of the vial (6) has an internal diameter of at least 7.5 mm.

Patentansprüche

1. Verfahren zur Herstellung einer vorgefüllten Spritze zur Verabreichung einer pharmazeutischen Zubereitung, wobei jene Spritze einen im wesentlichen zylindrischen Spritzenkörper (6) mit einem Hals an einem Halsende und eine in einem Rand (7) an einem mit einem Rand versehenen Ende endende Seitenwand, wobei wenigstens ein Bestandteil (A) der Zubereitung über das Halsende in den Körper (6) gefüllt und im Körper (6) mit einem elastomeren, den Körper am Halsende abschließenden und mit einer Kappe (4) gesicherten Verschluß (5) versiegelt wird und ein elastomerer Kolben (8) am mit einem Rand versehenen Ende eine hermetische Dichtung mit einer Innenfläche jener Seitenwand bildet, Nadelmittel (22) für eine Relativbewegung gegenüber der Kappe (4), um den elastomeren Verschluß (5) zu durchdringen, und Plungermittel (10) zur Verbindung mit einer Außenseite (16) des Kolbens umfaßt, dadurch gekennzeichnet, daß die Spritze hergestellt wird, indem Bauteile, einschließlich jener Plungermittel (10) und jener Nadelmittel (22), mit einer vorgefüllten Ampulle (6) verbunden werden, die hergestellt wird durch Ausbildung jenes Körpers mit einem solchen Höhen/Durchmesser-Verhältnis, daß der Körper stabil ist und daß jegliche äußere Erstrekkung des Randes (7) kein solches Ausmaß hat, daß sie zu Störungen führt, die ein Kippen verursachen wurden, wenn der Körper auf jenem Rand (7) stehend durch Einrichtungen zum Füllen und Überkappen von pharmazeutischen Ampullen befördert wird; Einsetzen jenes gesamten elastomeren Kolbens (8) in jenem mit einem Rand versehenen Ende des Körpers zur Bildung einer am Hals offenen Ampulle (6); und Füllen jener Ampulle durch jenen Hals mit jener pharmazeutischen Zubereitung (A) mit nachfolgender Aufbringung jenes elastomeren Verschlusses (5) und jener Kappe (4), während die Ampulle (6) auf jenem Rand (7) stehend durch Einrichtungen zum Füllen und Überkappen von pharmazeutischen Ampullen befördert wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß jener elastomere Verschluß so ausgebildet ist, daß er die Ampulle (6) belüftet, wenn er teilweise in jenen Hals eingesetzt ist, und jener elastomere Verschluß (60) in zwei Stufen aufgebracht wird, wobei in der ersten Stufe der Verschluß teilweise eingesetzt wird und die Ampulle (6) danach während der Lyophilisierung der darin eingefüllten pharmazeutischen Zubereitung belüftet bleibt und in einer zweiten Stufe nach der Lyophilisierung das Einsetzen des Verschlusses (60) abgeschlossen wird.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Verhältnis der Gesamthöhe des Körpers (6) zum Außendurchmesser seines Randes (7) 2,5:1 nicht überschreitet.

4. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Hals der Ampulle (6) einen Innendurchmesser von mindestens 7,5 mm aufweist.

Revendications

1. Procédé de fabrication d'une seringue préremplie pour l'administration d'une préparation pharmaceutique, ladite seringue comportant un corps de seringue (6) généralement cylindrique ayant un étranglement à une extrémité d'étranglement, et une paroi latérale se terminant en un rebord (7) à une extrémité à rebord, au moins un composant (A) de la préparation versé dans le corps (6) par l'extrémité d'étranglement et enfermé hermétiquement dans le corps (6) à l'aide d'une fermeture en élastomère (5) fermant le corps à l'extrémité d'étranglement et fixée par un couvercle (4), et un piston en élastomère (8) à l'extrémité à rebord, formant un joint hermétique avec une surface intérieure de ladite paroi latérale, un moyen à aiguille (22) pour effectuer un mouvement par rapport au couvercle (4) afin de pénétrer à travers la fermeture en élastomère (5), et un moyen poussoir (10) pour la connexion à un côté externe (16) du piston, caractérisé en ce que la seringue est fabriquée en associant des composants comprenant ledit moyen poussoir (10) et ledit moyen à aiguille (22) avec un flacon prérempli (6) fabriqué: en formant ledit corps avec un rapport hauteur/diamètre tel que le corps soit stable, et de sorte que toute projection du rebord (7) vers l'extérieur soit insuffisante pour provoquer des interférences, telles que pouvant être occasionnées par un renversement lorsque l'on fait passer le corps en position debout sur ledit rebord (7) à travers des équipements de remplissage et de bouchage de flacons pharmaceutiques; en insérant ledit piston en élastomère (8) entièrement à l'intérieur de ladite extrémité à rebord du corps, pour former un flacon (6) ouvert au niveau de l'étranglement; et en remplissant ledit flacon par ledit étranglement avec ladite préparation pharmaceutique (A), puis en appliquant ladite fermeture en élastomère (5) et ledit couvercle (4), tout en faisant passer le flacon (6) en position debout sur ledit rebord (7) à travers des équipements de remplissage et de bouchage de flacons pharmaceutiques.

2. Procédé selon la revendication 1, caractérisé en ce que ladite fermeture en élastomère a une forme conçue pour aérer le flacon (6) lorsqu'elle est partiellement insérée dans ledit étranglement, et en ce que ladite fermeture en élastomère (60) est appliquée en deux étapes, dans la première desquelles la fermeture est insérée partiellement et le flacon (6) demeure alors encore aéré pendant la lyophilisation de la préparation pharmaceutique qui y est versée, et une deuxième étape après la lyophilisation dans laquelle la fermeture (60) est insérée complètement.

3. Procédé selon la revendication 1 ou 2, caractérisé en ce que le rapport de la hauteur globale du corps (6) au diamètre extérieur de son rebord (7) ne dépasse pas 2,5:1.

4. Procédé selon l'une quelconque des revendications précédentes, caractérisé en ce que l'étranglement du flacon (6) a un diamètre interne d'au moins 7,5 mm.

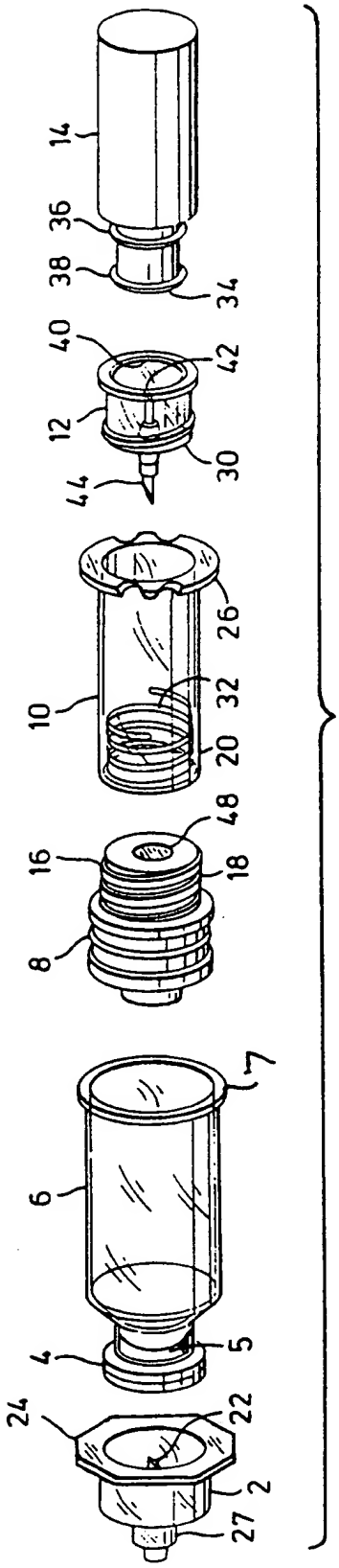

14
36
38
34
40
42
12
30
44
26
10
32
20
48
16
18
8
7
6
4
5
24
22
2
27

FIG. 1

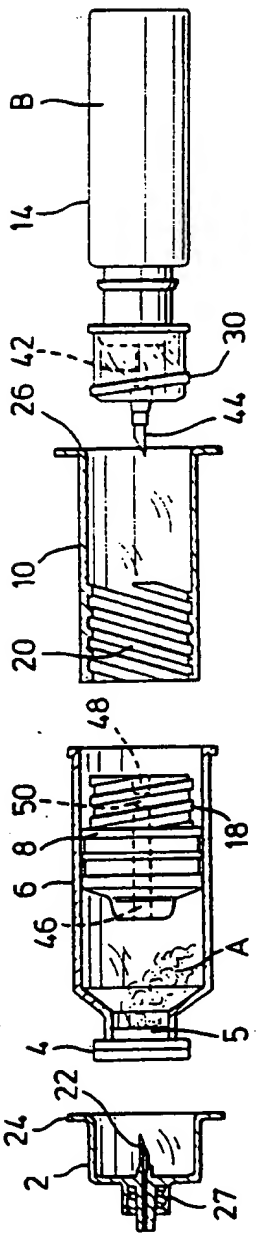

B
14
42
30
26
44
10
20
48
50
18
8
6
46
A
4
5
22
24
2
27

FIG. 2

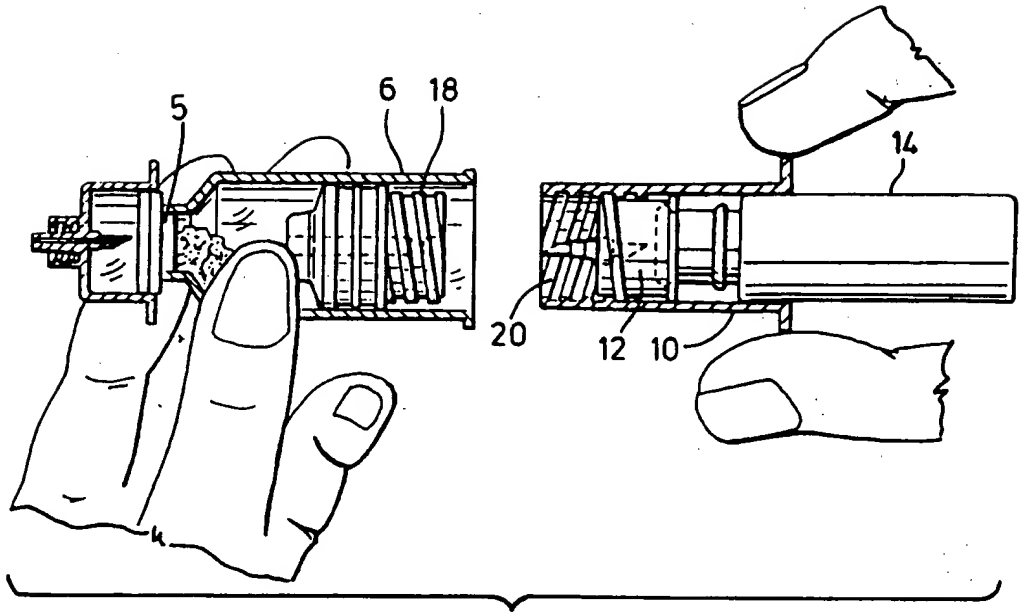


FIG. 3

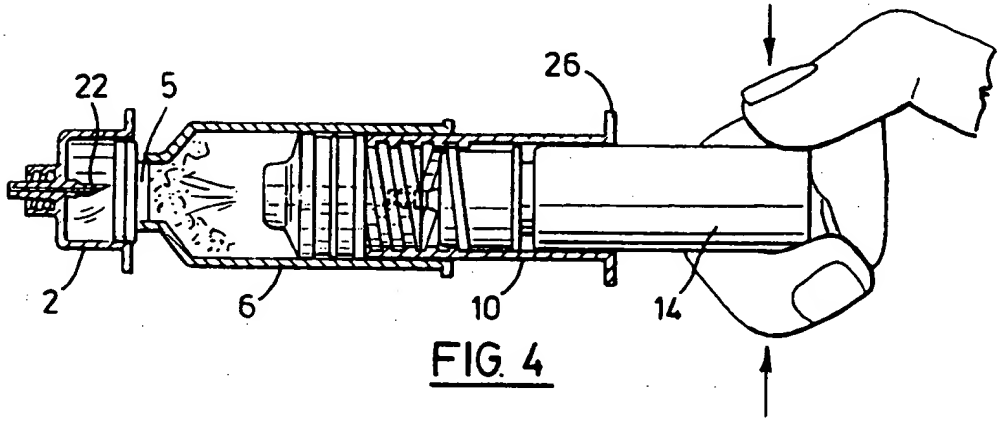


FIG. 4

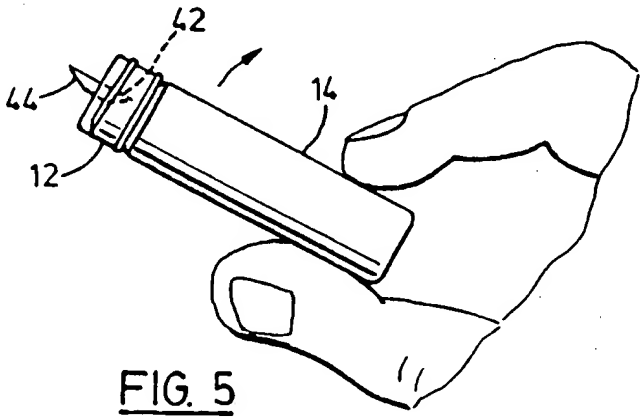


FIG. 5

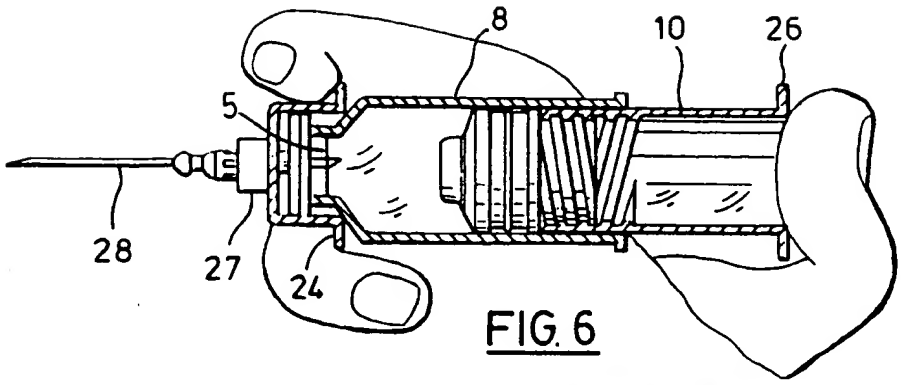


FIG. 6

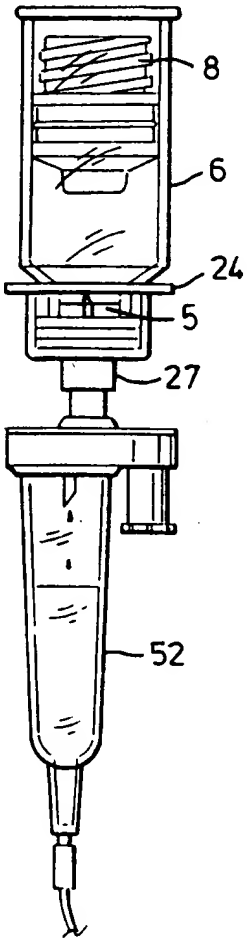


FIG. 7

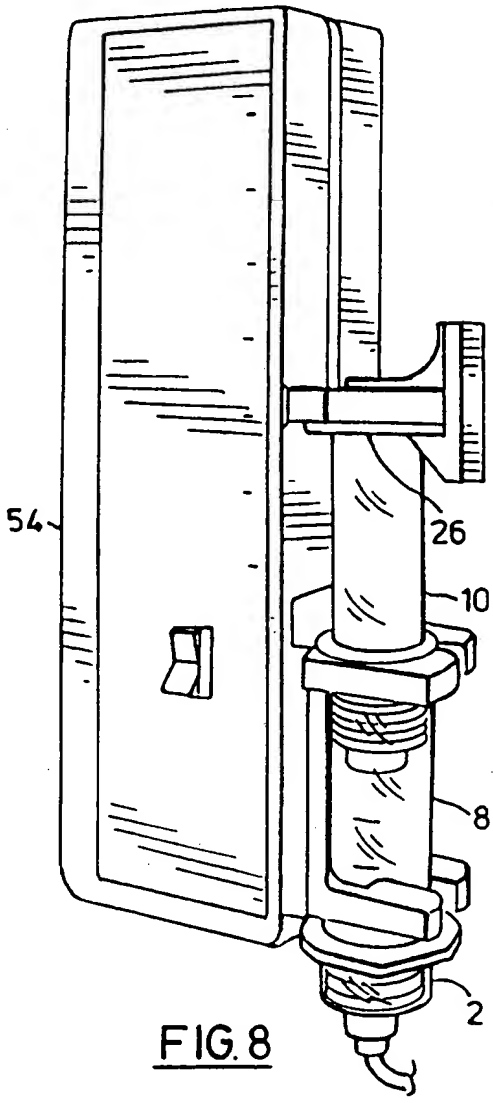
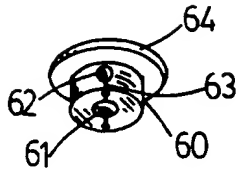


FIG. 8

FIG. 9



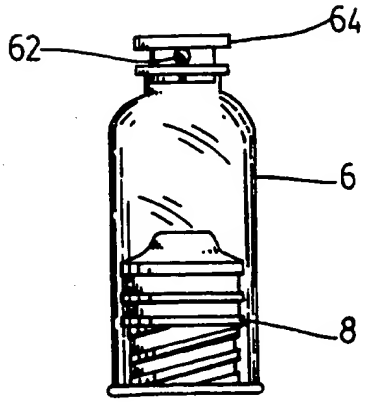


FIG. 10

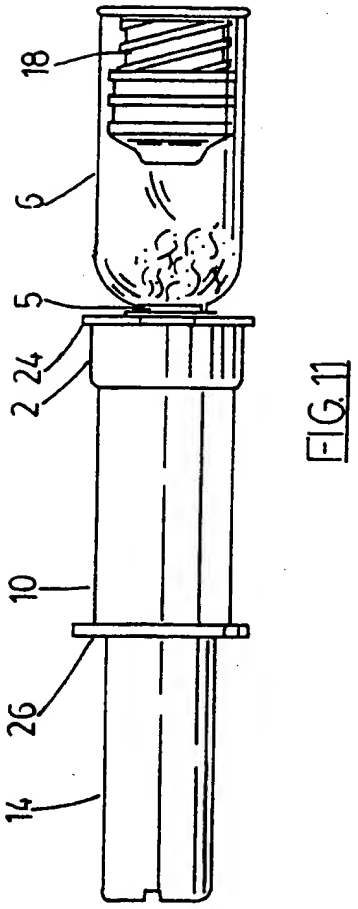


FIG.11

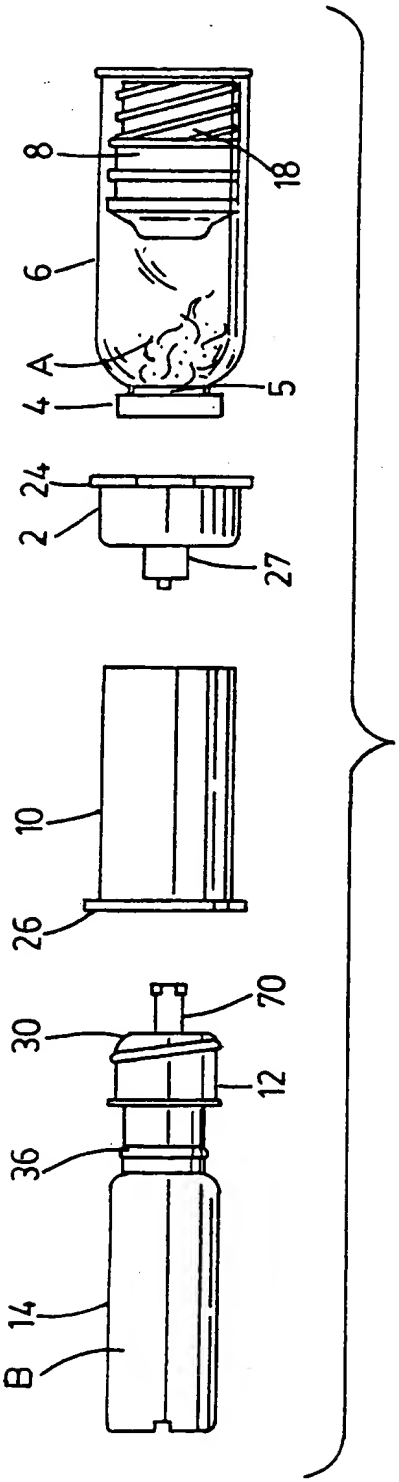


FIG.12